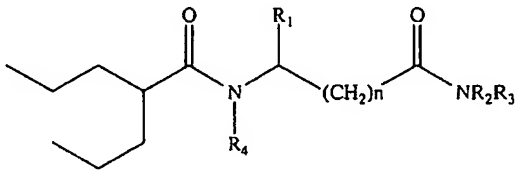
REMARKS

Claims 1-10, 47, and 93-101 are pending in this application. Claims 11-46 and 48-92 have been canceled without prejudice or disclaimer.

Pending claim 1 is directed to a "method of treating a subject suffering from pain comprising periodically administering to the subject a therapeutically effective dose of a compound having the following structure:



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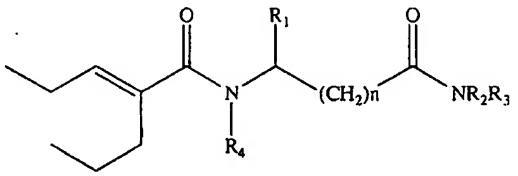
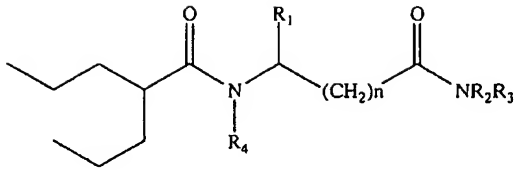


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the therapeutically effective dose is 1,000 to 6,000 mg; so as to thereby treat the subject's pain." Claims 2-10, 100 and 101 depend, either directly or indirectly, from claim 1.

Independent claim 47 is directed to a "method of pain prophylaxis in a subject predisposed to suffering from pain comprising periodically administering to the subject a prophylactically effective dose of a compound having the following structure:



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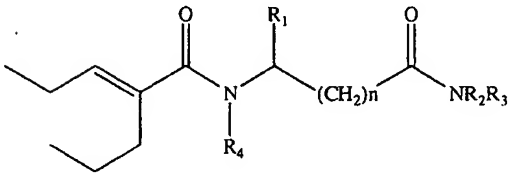
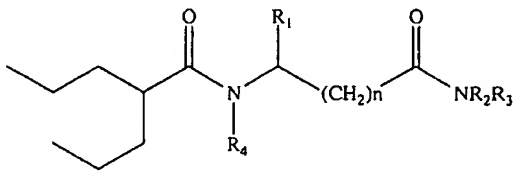


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the prophylactically effective dose is 1,000 to 6,000 mg; and wherein the pain is neuropathic pain, a migraine or a headache disorder; so as to thereby effect pain prophylaxis in the subject."

Claim 93 is directed to a "method of treating a subject comprising periodically administering to the subject a pharmaceutical composition comprising a therapeutically effective dose a compound having the following structure:



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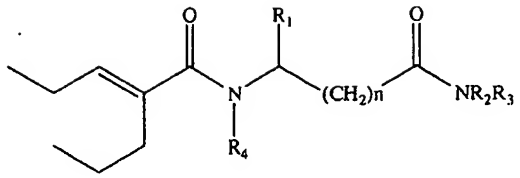
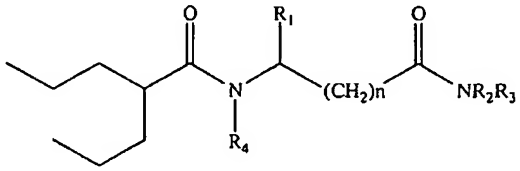
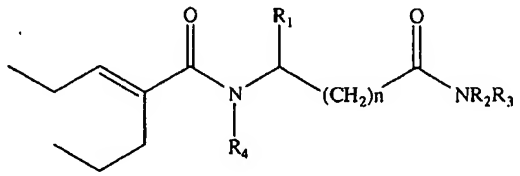


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to a and less than or equal to 3, and a pharmaceutically acceptable carrier; wherein the therapeutically effective dose is 1,000 to 6,000 mg; and wherein the pain is neuropathic pain, a migraine or a headache disorder; so as to thereby treat the subject's pain."

Present claim 94 is directed to a "method of pain prophylaxis in a subject predisposed to suffering from pain comprising periodically administering to the subject a composition comprising a prophylactically effective dose of a compound having the following structure:

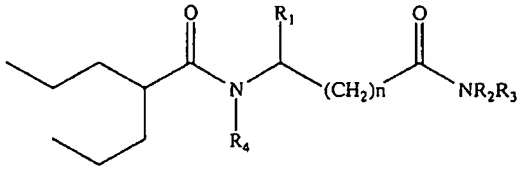


or

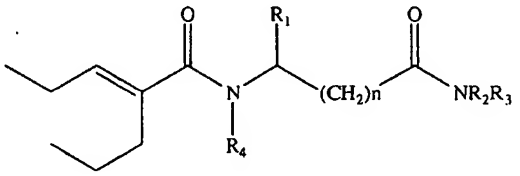


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, and a pharmaceutically acceptable carrier; wherein the therapeutically effective dose is 1,000 to 6,000 mg; and wherein the pain is neuropathic pain, a migraine or a headache disorder so as to thereby effect pain prophylaxis in the subject."

Claim 95 is directed to a "method of treating a subject suffering from a headache disorder comprising periodically administering to the subject a therapeutically effective dose of a compound having the following structure:

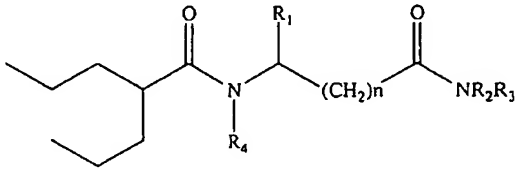


or



wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the therapeutically effective dose is 1,000 to 6,000 mg; so as to thereby treat the headache disorder." Claim 97, 98 depend, either directly or indirectly, from claim 95.

Claim 96 is directed to a "method of preventing a headache disorder in a subject predisposed to suffering from a headache disorder comprising periodically administering to the subject a prophylactically effective dose of a compound having the following structure:



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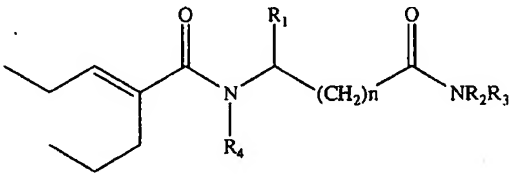
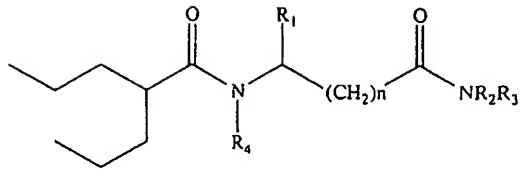
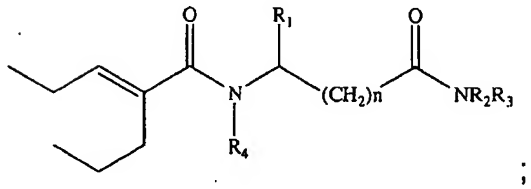


wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; wherein the prophylatically effective dose is 1,000 to 6,000 mg; so as to thereby prevent the headache disorder in the subject." Claim 99 depends from claim 96.

Accordingly, each of the presently pending claims are directed, generally, to methods of treating subjects suffering from various pain, methods of treating subjects suffering from headache disorders, methods of preventing pain, methods of preventing headache or methods of pain prophylaxis, comprising administering an effective amount of a dose of a compound having one of the following structures:



or



;

wherein R_1, R_2, R_3 and R_4 are independently the same or different and are hydrogen, a linear or branched C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3, wherein the effective dose is in the amount of 1,000 to 6,000 mg.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, claims 1-10, 47 and 93-101 have been rejected under 35 USC § 103(a) as being unpatentable over Bialer et al. (US Patent No. 5,585,358) and IE 0052415 ("the '415 patent") in view of Hansen et al., McQuay et al., Shank et al., Carrazana et al., Magnus et al., and Zakrzewska et al. and the Merck Manual (all references of record).

The Examiner asserts that it would have been obvious to employ N-(2-n-propylpentanoyl) glycinamide or the compounds of the '415 patent, in the claimed dosage and dosing regimen, in a method of treating pain in the presently claimed routes of administration

In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because the Examiner has applied impermissible hindsight to glean the essence of the present subject matter from the cited art.

As explained in MPEP § 2141.01(III), the content of the cited art is to be determined at the time the invention was made in order to avoid hindsight. The requirement "at the time the invention was made" is to avoid impermissible hindsight. "It is difficult but necessary that the decisionmaker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the **art. >...<" W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Applicants respectfully submit that a person skilled in the art would know that the characterization of a compound as having a specific activity, e.g., the ability to treat pain, particularly at a given dosage, can be made only where the compound has been tested and found to have such activity. The mere assumption that a group of compounds, which have certain properties, will also exhibit additional activities, similar or identical to other compounds of a similar structure, is improper without scientific evidence in support thereof.

With regard to the present application, Applicants submit that valproic acid containing anti-epileptic-drugs (AEDs) are not generally effective as pain reducing agents. Although reports may classify the AEDs as analgesics, as known to the skilled artisan at the time the present subject matter was invented, only a few of several AEDs had been

shown to be effective in the treatment of pain.

Applicants respectfully submit that a person of ordinary skill in the art at the time the present application was filed would not have been able to arrive at the presently claimed subject matter. More specifically, Applicants respectfully submit that a prima facie case of obviousness has not been set forth because the Examiner's assertions are the result of improper hindsight.

As evidence of the aforementioned, Applicants submit herewith a copy of Drewes et al., "Valproate for treatment of chronic central pain after spinal cord injury, a double blind cross-over study," *Paraplegia*, 32(8): 565-569 (1994). Drewes et al. describe a double-blind placebo controlled study of valproate for the treatment of chronic central pain following spinal cord injury. In discussing the results of the study, Drewes et al., indicate that:

> [i]n this study ***we could not demonstrate significant analgesic effects of valproate***. The study group had severe tingling, shooting and cutting pain below the level of injury with pain onset a few months after SCI, which is typical for central pain. The pain was severe and constant, and several analgesics were tried without benefit, confirming that the management of pain in the patient group should be considered to be difficult. The dose of valproate was considered sufficient for effect as serum concentrations reached the upper limit during the last treatment week in most patients; thus a beneficial effect should be expected. Thirty three per cent improved during valproate treatment, but no statistically significant effect was observed compared to the placebo series." (Emphasis Added). Please *see* page 568, left column, 2nd paragraph.

Drewes et al. conclude that "...***valproate cannot be recommended for severe central pain***." (Emphasis Added). Please *see* Drewes et al. at page 568, right column, 2nd paragraph.

As shown in Drewes et al., not all anticonvulsants drugs may also be useful in the treatment of pain. In fact, Applicants submit that Drewes et al. provides evidence that, ***a person of ordinary skill in the art would not consider VPA derivatives effective for treating pain***. Accordingly, Applicants respectfully submit that the Examiner's assertion, that one of ordinary skill in the art at the time of the invention would have found it obvious to employ N-(2-n-propylpentanoyl) glycinamid in a method of treating and prophylaxis of pain is the result of impermissible hindsight. Please *see* the Official Action at page 5, paragraph 2. In this regard, Applicants submit that Drewes et al., presents a clear scientific doubt regarding the success of such a use.

Additionally, Applicants submit that only a few of the so-called 2nd generation VPA derivatives, including amide derivatives of VPA, exhibit a significant pain attenuation capability. As evidence of the aforementioned, Applicants submit herewith Winkler et al., "Efficacy of antiepileptic isomers of valproic acid and valpromide in a rat model of neuropathic pain," *Br J Pharmacol.*, 146(2):198-208 (20005). Winkler et al. conclude that in a rat model of neuropathic pain, MVPD (a VPA amide analogue) was not efficient in attenuating pain. Similarly, the pain attenuating effect of valpromide (VPD), an agent commonly used in the treatment of epilepsy, drastically diminished 60 min after dosing at doses which were 1.5 fold of those used for VCD. *See*, generally, Winkler et al. In

contrast, as shown in figures 2 and 3 of Winkler et al., the valnoctamide (VCD) exerts a significant pain attenuating effect which is maintained for a long time period. *See* Winkler et al. at figures 2 and 3.

Accordingly, Applicants respectfully submit that a person of ordinary skill in the art would not have expected compounds used in the methods of the present claims to exhibit a prolonged pain attenuating effect particularly where VPA derivatives have. In particular, Applicants note that VPA derivatives which have, for example, a short plasma half life and require large doses for achieving even a transient pain attenuating effect would not have been expected to be effective against pain.

In addition, Applicants submit that of the over 30 or more AEDs tested as analgesics, only Gabapentin and Pregabalin have been approved by the FDA for pain. A vast number of other drugs have not been approved, mainly because the analgesic activity was not clinically proven. For example, topiramate, a known AED, exhibited substantially no analgesic activity according to a report issued by Dr. C.W. Martin, a senior medical advisor of the Workers Compensation Board of British Colombia. In the report, a copy of which is enclosed herewith, Dr. Martin concludes that "...there is no high level of evidence to support the efficacy of Topiramate in treating naturopathic pain." *See,* generally, the Martin Report.

Applicants respectfully submit that, as evidenced by the publications submitted herewith, a person of ordinary skill in the art at the time the present application was filed would not have been able to arrive at the present subject matter. More specifically,

Applicants respectfully submit that a prima facie case of obviousness has not been set forth because the Examiner's assertions are the result of improper hindsight.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, the cited art does not render the presently pending claims obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

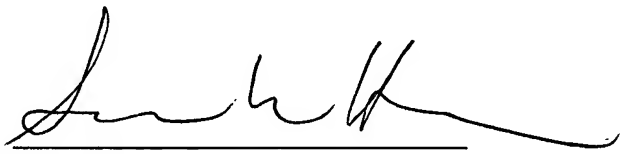
CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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